Original Article

Chemotherapy-based Control of Ascariasis and Hookworm in Highly Endemic Areas of China: Field Observations and a Modeling Analysis*

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Abstract

Objective Our objective was to systematically evaluate chemotherapy-based control of ascariasis and hookworm infection and make predictions of the effectiveness of repeated mass treatment at different levels of coverage in highly endemic areas of China.

Methods Field surveys were carried out to acquire the ascariasis and hookworm prevalence and intensity (mean worm burden) at baseline, one month and one year later. We calculated model parameters based on the survey data, then incorporated them into a quantitative framework to predict the prevalence and intensity one year later. Sensitivity analyses were performed to assess the influence of the chemotherapy measures on prevalence and intensity, and model simulations were performed to evaluate the feasibility of achieving the proposed transmission control criteria under different chemotherapy measures.

Results The predicted prevalence and intensity one year from baseline were within the 95% confidence interval of actual values. As treatment frequency or coverage increased, the prevalence and intensity decreased. Model simulations show that many rounds of treatment are needed to maintain the prevalence at a low level in highly endemic areas of China.

Conclusion We should select different combinations of treatment frequency, coverage and drug efficacy according to available resources and practical attainable conditions. Mathematical modeling could be used to help optimize the chemotherapeutic scheme aiming at specific parasitic species and areas, and to direct the establishment of soil-transmitted helminthiasis control criteria in China.

Key words: *Ascariasis*; Hookworm; Chemotherapy; Field survey; Mathematical modeling

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INTRODUCTION

Ascaris lumbricoides (roundworm), *Ancylostoma duodenale* and *Necator americanus* (hookworm), the main soil-transmitted parasitic nematodes, are widely distributed throughout the tropics and subtropics of the world, causing human physical and intellectual growth retardation[1]. China is one of the countries with the greatest burden of infections from these nematodes[2-3]. China's 2003 national survey of soil-transmitted helminth infections indicated that the prevalence of ascariasis and hookworm is 12.72% and 6.12%, respectively, and although it decreased

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compared with the 1990 estimates, a high prevalence remains in some areas[4-5]. It is estimated that 125 million people are infected with soil-transmitted nematodes in China[2].

Chemotherapy is advocated as an affordable and effective control measure for reducing intestinal nematode infections[6-8]. Different chemotherapy measures have been used to control ascariasis and hookworm disease in China[9-10], although a theoretical evaluation of these programs is absent. How deworming influences the reinfection process, and how different deworming strategies affect the infection level (prevalence and intensity) are questions that need to be answered[11-13]. China is now establishing criteria for the control and elimination of soil-transmitted helminthiasis, which also calls for evaluating chemotherapeutic schemes in areas with different infection rates[14-15].

Because conducting a controlled field trial to evaluate a disease control program is infeasible, mathematical modeling of disease transmission is an important tool for predicting and evaluating the public health impact of field interventions on relevant indicators over time[16-17]. Few mathematical modeling studies on ascariasis and hookworm infection and reinfection in China are reported. We implemented a field cohort study in 2008-2009 and conducted a modeling analysis, in an attempt to predict and evaluate the soil-transmitted helminthiasis chemotherapy control effect, and to help establish control and elimination criteria in China.

MATERIALS AND METHODS

Field Survey

The field surveys were carried out in two highly endemic sites: Cuiping District of Yibin City in Sichuan Province (hereinafter abbreviated as “Cuiping of Sichuan”) and Jinxian County in Jiangxi Province (hereinafter abbreviated as “Jinxian of Jiangxi”). The soil-transmitted helminth infection rate of the two sites is more than 20%, according to the 2003 national survey. The two sites were selected on the criteria that (1) no intervention activities were conducted in the previous year; and (2) the population proportion of children under 14 years was not more than one-third. The subjects were the resident population between 5 and 70 years old.

The field survey was an interventional cohort study lasting for one year. Subjects were investigated and followed up at 0, 1, and 12 months. All subjects were given a single dose of 10 mg/kg body weight of Pyrantel Pamoate for two days at baseline and at the 12 month follow-up. A detailed survey procedure flowchart is displayed in Figure 1.

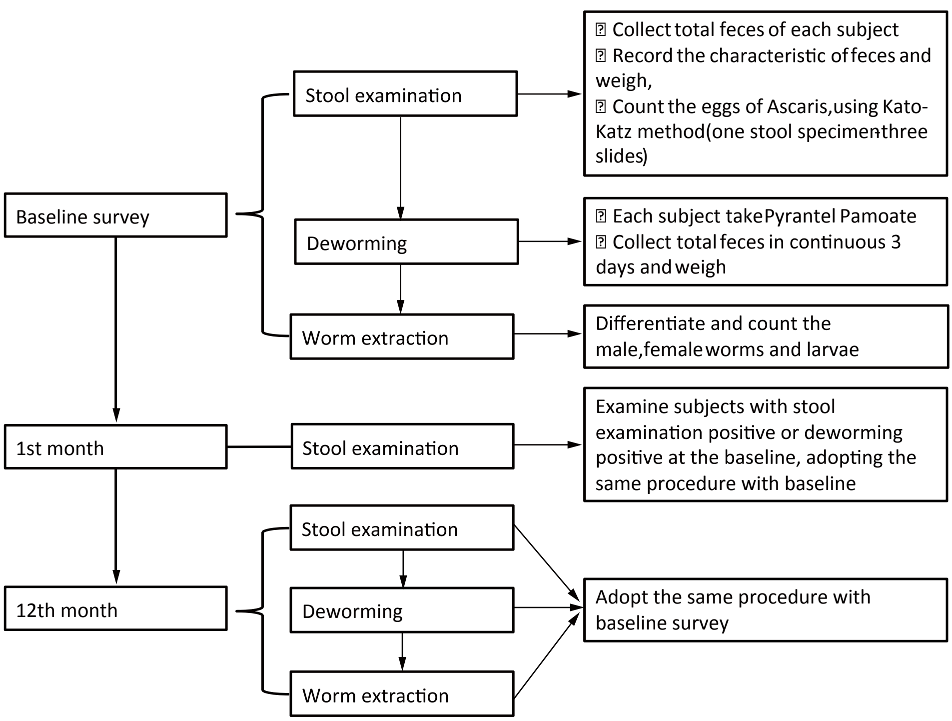


Figure 1. Field survey procedure flowchart.

We obtained ascariasis and hookworm infection data from the two sites as: (1) infection rate and mean worm burden at baseline, (2) infection rate after one month, and (3) infection rate and mean worm burden after one year.

Modeling Analysis

The Models We used the quantitative framework developed by Medley to model ascariasis and hookworm reinfection after rounds of chemotherapy intervention. The framework is a quantitative study of the dynamic relationship between parasite burden, development of disease and chemotherapy application[18-19].The models are introduced briefly here.

The host population is divided into a discrete number of "types", each with a rate of establishment relative to the whole population, h_j, and proportional representation in the population, ω_j.

Modeling the effect of treatment on population dynamics

$$\frac{dW}{dt} = \mu R_0 f(W;k,\gamma) - \mu W \qquad (1)$$

W represents the total mean parasite burden, sum of the mean burden of surviving worms and worms established since treatment. R_0 is the basic reproductive rate and μ is the *per capita* death rate of the parasites. The function $f(W;k,\gamma)$ represents the density-dependent effects.

Modeling the effect of treatment on the distribution of parasites The probability distribution of all parasites at time *t* after treatment is:

$$p_{nj}(t) = \sum_{r=0}^{n} q_{rj}(t) s_{n-r,j}(t) \qquad (2)$$

This is a convolution of the surviving parasite distribution, $s_{nj}(t)$, and the reinfection parasite distribution $q_{nj}(t)$. The $q_{nj}(t)$ follows a Poisson distribution, while $s_{nj}(t)$ is the sum of terms from a series of binomial distributions:

$$s_{nj}(t) = \sum_{r=n}^{n_{max}} s_{rj}(0) B(n;r,e^{-\mu t}) \qquad (3)$$

$s_{rj}(0)$ describes the distribution of surviving parasites immediately after treatment, given as:

$$s_{rj}(0) = (1-c)p_{nj} + c\sum_{r=n}^{n_{max}} B(n;k,\alpha)p_{rj} \qquad (4)$$

C is the proportion of hosts treated and α is drug efficacy $B(n;r,\alpha)$ represents the probabilities of having *n* parasites when *r* parasites are treated. p_{nj} is the existing (pre-treatment) parasite distribution in host type *j*.

Model Parameter Estimation The actual cohort data were used to calculate the following parameters, the estimation methods of which were not described by Medley.

Density dependence parameter *γ* The dependence of egg production on worm burden is described empirically by an exponential decay function[20-23],

$$\lambda_n = \lambda_0 e^{-\gamma n}, Z = e^{-\gamma} \qquad (5)$$

n is the number of the worms harbored by a host, λ_0 is the egg production by coupled worms, and the egg production per female worm when a host harbored *n* mature worms.

The density-dependent constraint on worm fecundity *Z* should be less than 1, and nearer to 1 when the density-dependence effect is higher. In practice it could be calculated as more than 1, due to drug efficacy or some other reason, therefore we modified equation (5) as follows:

$$\lambda_{\bar{n}} = \lambda_0 e^{-\gamma \bar{n}}, Z = e^{-\gamma} \qquad (6)$$

$\bar{n}$ represents the mean worm burden of persons with female worms; $\lambda_{\bar{n}}$ is the average number of eggs produced by each female worm in persons with female worms; and λ_0 is the eggs produced by one couple parasite, which is based on the persons who harbored only one male and one female parasite (excluding those with two male worms or two female worms).

Negative binomial distribution parameter k Assuming that the distribution of parasites in the whole community follows a negative binomial distribution at the equilibrium state, the over-dispersion parameter *k* can be derived from the following equation[24]:

$$p = 1 - (1 + \frac{W}{k})^{-k} \qquad (7)$$

W is the mean worm burden of all of the subjects and *p* is the infection rate at baseline.

Basic reproductive rate R_0 The density-dependence effect is determined by the equation below when the distribution of parasites follows a negative binomial distribution[18].

$$f(W;k,\gamma) = W[1 + \frac{W}{k}(1 - e^{-r})]^{-(k+1)} \qquad (8)$$

When the endemic infection is stable, denoting

dW/dt = 0, R_0 can be derived from the following equation:

$$W^* = \frac{(R_0^{\frac{1}{K+1}} - 1)K}{1 - Z} \quad (9)$$

W^* represents the equilibrium worm burden, namely the baseline mean worm burden.

Estimation of the actual infection rate of the total population after one year When treatment coverage is low, we suppose that the population who did not receive treatment received negligible benefits from those who received treatment, and that they have the same infection rate after one year as they did at baseline. We estimated the actual infection rate of the total population after one year as: Infection rate of total population at 12th month = treatment coverage×infection rate of survey population at 12th month + (1 - treatment coverage) × baseline infection rate of survey population.

Model Validation Actual observed data at one-year of follow-up was used for model validation.

Sensitivity Analysis We changed the values of the model parameters related to the chemotherapy measure to examine their influences on prevalence and intensity. Univariate and multivariate analyses were performed, including the parameters of treatment frequency, treatment coverage and drug efficacy.

Model Simulations Following the current commonly-adopted chemotherapy frequency of once per year and coverage of 60% or 80% in China, model simulations were performed to evaluate the feasibility of establishing the proposed transmission control criteria, which were set as 3% for ascariasis prevalence and 1% for hookworm prevalence.

Software

SAS 9.2(SAS Institute Inc.,USA) was used for statistical analysis, and Matlab 7.11.0(The Mathworks Inc.,USA) was used for modeling and simulations.

Ethics Statement

The field study protocol was approved by the National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention (Shanghai, China). The participants were informed that the procedure did not pose any potential risk and their identities and personal particulars would be kept strictly confidential. During the field survey, parents and their children were informed that their participation was voluntary and that they could withdraw from the study at any time without consequence. Consent of those who agreed to participate was taken either in written form (signed) or verbally followed by their thumb prints (for those who were illiterate), and from parents or guardians (on behalf of their children).

RESULTS

Field Survey

Both the prevalence and intensity of ascariasis and hookworm infection at baseline in Cuiping of Sichuan were higher than those in Jinxian of Jiangxi.

The ascariasis infection rates of Cuiping of Sichuan and Jinxian of Jiangxi changed from 28.79% and 20.35%, respectively, at baseline to 30.10% and 7.51% after one year, with the mean worm burden changing from 1.32 and 0.65 to 1.04 and 0.56, respectively.

The hookworm infection rates of Cuiping of Sichuan and Jinxian of Jiangxi changed from 24.38% and 18.69%, respectively, at baseline to 18.02% and 4.19% after one year, with mean worm burden changing from 5.81 and 1.82 to 4.48 and 1.41, respectively (Table 1).

Table 1. Infection Rate and Mean Worm Burden before and after Chemotherapy at the Two Survey Sites

Survey Site	Infection	Baseline			1st Month		12th Month		
		n	IR (%)	MWB	*n*	IR (%)	*n*	IR (%)	MWB
Cuiping of Sichuan	Ascariasis	771	28.79	1.32	579	4.46	505	30.10	1.04
	Hookworm		24.38	5.81		7.43		18.02	4.48
Jinxian of Jiangxi	Ascariasis	1022	20.35	0.65	941	0.97	812	7.51	0.56
	Hookworm		18.69	1.82		4.67		4.19	1.41

Note. *n*=persons examined, IR=infection rate, MWB=mean worm burden.

Model Parameter Estimation

The basic reproductive rate (R_0) of ascariasis and hookworm in Cuiping of Sichuan was 2.95 and 2.94, respectively, which was higher than that in Jinxian of Jiangxi (2.31 and 2.46). The over-dispersion parameters (*k*) of the two sites were similar for the two infections. The γ value of ascariasis was higher than that of hookworm, i.e., the severity of density-dependent constraint on hookworm fecundity was higher than that of ascariasis in the two sites (Table 2).

Model Validation

Table 3 shows that the predicted theoretical results after one year, including infection rate and mean worm burden, are within the 95% confidence intervals (CI) of the actual survey values.

Table 2. Model Parameter Values

Parameters	Cuiping of Sichuan		Jinxian of Jiangxi	
	Ascariasis	Hookworm	Ascariasis	Hookworm
Life expectancy of mature worms (years)[2,25]	1	3	1	3
Maximum worm burden observed in a person in the survey (n_{max})	70	600	50	210
Treatment coverage (*c*)	0.3200	0.3200	0.2800	0.2800
Drug efficacy (α)*	0.8500	0.7000	0.9500	0.7500
Basic reproductive rate (R_0)	2.9500	2.9400	2.3100	2.4600
Over-dispersion parameter (*k*)	0.1480	0.0612	0.1245	0.0601
γ value	0.1927	0.0188	0.2376	0.0453
Severity of density-dependent constraint on worm fecundity *Z*	0.8247	0.9814	0.7885	0.9557

Note. *Drug efficacy Is calculated is (baseline infection rate - 1st month infection rate after chemotherapy) / baseline infection rate.

Table 3. Comparison of Actual and Theoretical Values of Infection Rate and Mean Worm Burden after One Year

Survey Sitesand Species		IR (%)			MWB		
		AV	95%CI of AV	TV	AV	95%CI oAV	TV
Cuiping of Sichuan	A. lumbricoides	29.21	24.72-33.70	25.03	1.26	0.87-1.65	1.04
	Hookworm	22.34	18.47-26.21	20.80	4.05	2.79-5.31	4.48
Jinxian of Jiangxi	A. lumbricoides	16.75	14.41-19.09	17.45	0.53	0.42-0.64	0.56
	Hookworm	14.63	12.64-16.62	14.97	1.35	0.88-1.82	1.41

Note. IR=Infection Rate, MWB=Mean Worm Burden, AV=Actual Value, CI=Confidence Interval, TV=Theoretical Value.

Sensitivity Analysis

Univariate Analysis Take ascariasis infection in Cuiping of Sichuan as an example of the univariate analysis results. Figure 2(a) shows that the extent of deceased prevalence and intensity with biannual treatment is larger than that of annual treatment. Figure 2(b) shows that the lower treatment coverage, the higher reinfection level with faster ascending velocity during the first year, followed by stable parallel trends. Figure 2(c) shows that the pattern of prevalence changes differs from that of intensity under different drug efficacy scenarios. High drug efficacy leads to more reductions in prevalence and intensity than low drug efficacy. For prevalence, during the first year, high drug efficacy has the fastest ascending velocity, followed by trends with almost the same velocity with low drug efficacy. For intensity, the four curves remain almost parallel.

In conclusion, treatment frequency and coverage influence the change in prevalence and intensity more than drug efficacy.

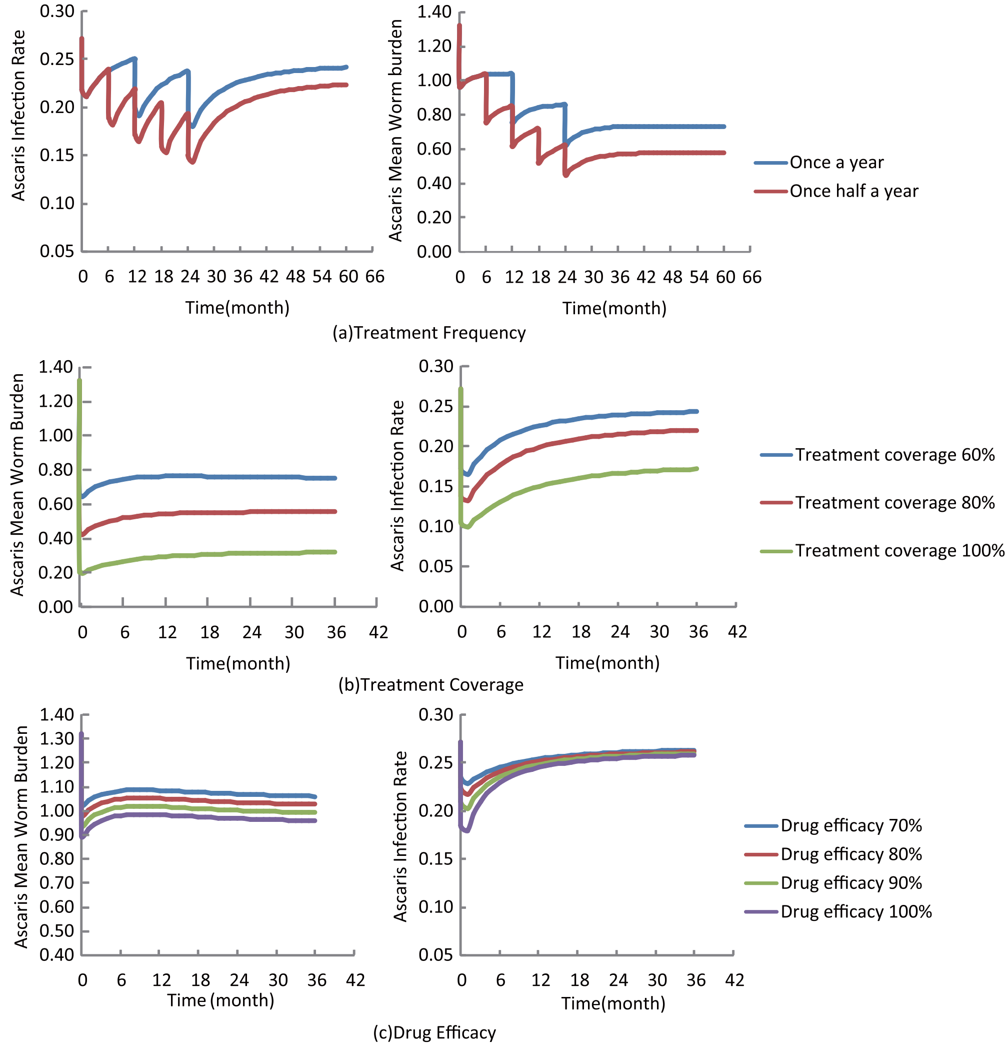


Figure 2. The influence of different measures (Cuiping of Sichuan as example).

Multivariate Analysis Because drug efficacy had less influence on prevalence and intensity, only treatment coverage and frequency are included in the multivariate analysis of the two infections and two survey sites (Figures 3 and 4).

Despite lasting one more year of treatment (36 months compared with 24 months), the descending extent of prevalence and intensity under annual treatment is still less than that under biannual treatment.

The infection level gap between treatment coverages of 60% and 80% is bigger than that between 80% and 100%. If treatment coverage increases from 60% to 80%, the infection level descends dramatically and remains low over the following three years.

Chemotherapy has a greater effect on prevalence than on intensity. The ascending velocity of intensity after each round of treatment is lower than that of prevalence, which is especially obvious for hookworm reinfection.

The reinfection velocity of ascariasis is faster than that of hookworm. The rounds of chemotherapy needed to reduce the prevalence and intensity to the same level in different sites are different.

Model Simulations

Take hookworm infection rate in Jinxian of Jiangxi as an example. Figure 5(a) shows that it would take nine rounds of annual treatment to reach a 1% infection rate

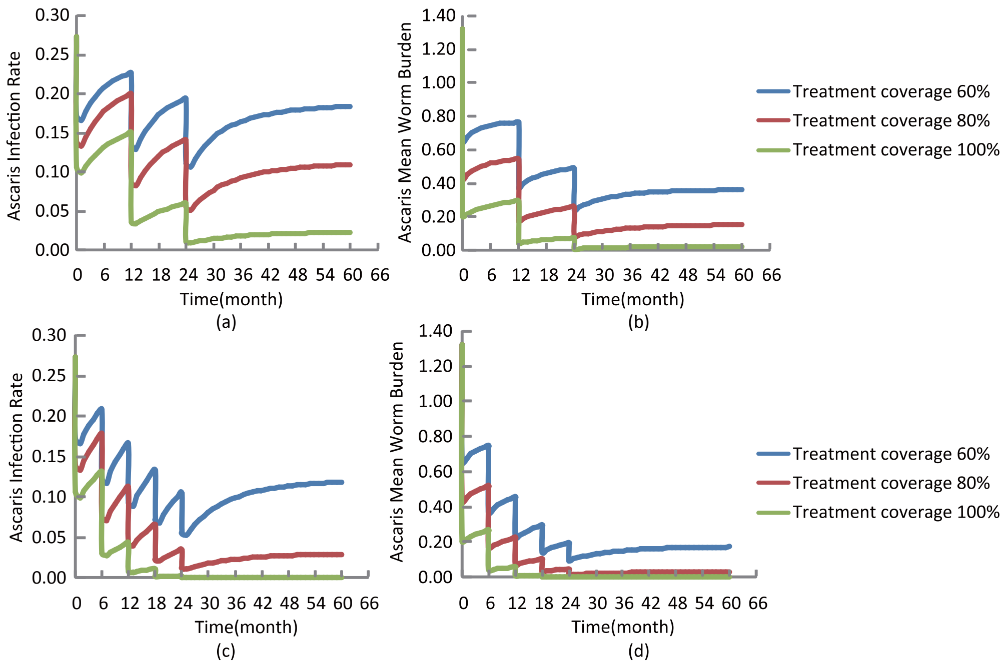


Figure 3. Comparison of the influences of different treatment coverages and frequencies on ascariasis infection in Cuiping of Sichuan. ***Note.*** (a) and (b) show the changes in ascariasis infection rate and mean worm burden with time under three levels of treatment coverage and annual treatment three times in two years, while (c) and (d) show biannual treatment five times in two years.

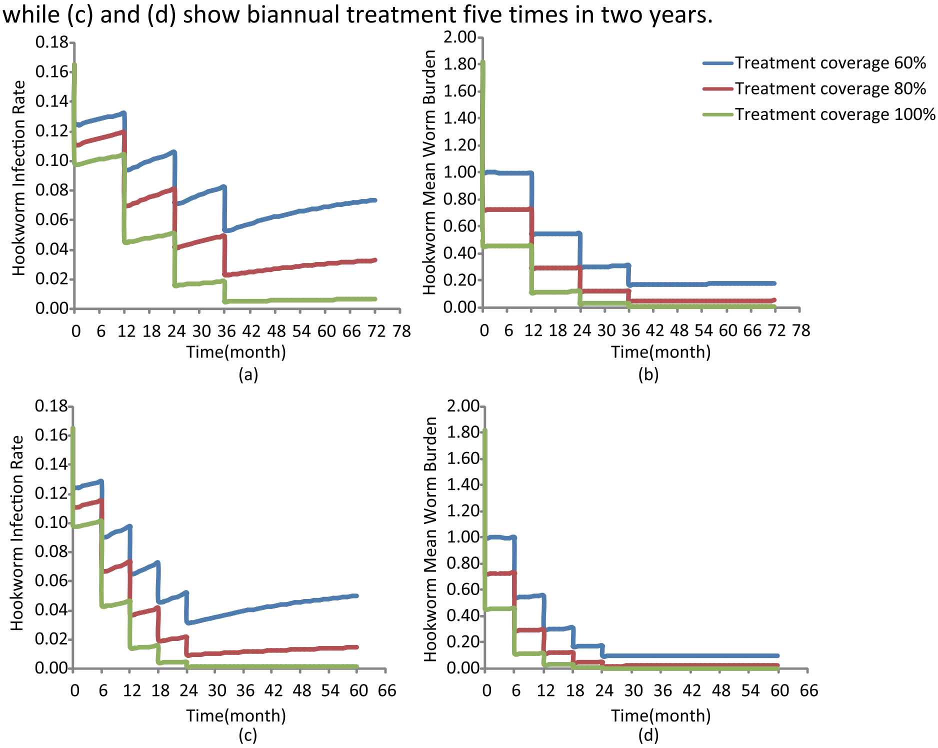
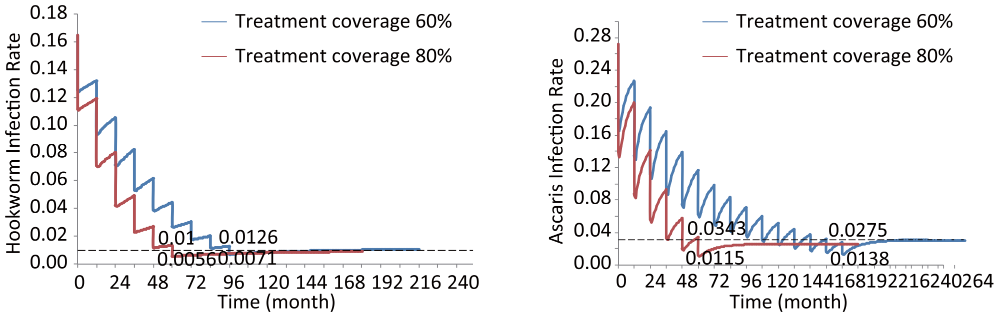


Figure 4. Comparison of the influences of different treatment coverages and frequencies to hookworm infection in Jinxian of Jiangxi. ***Note.*** (a) and (b) show the changes in hookworm infection rate and mean worm burden with time under three levels of treatment coverage and annual treatment four times in three years, while (c) and (d) show biannual treatment five times in two years.

under 60% treatment coverage, while only six rounds under 80% treatment coverage would be required.

Take ascariasis infection rate in Cuiping of Sichuan as an example. Figure 5(b) shows that it would take 15 rounds of annual treatment to reach a 3% infection rate under 60% treatment coverage, while only six rounds under 80% treatment coverage would be required.



(a) Hookworm infection in Jinxian of Jiangxi (b)Ascariasis infection in Cuiping of Sichuan

Figure 5. Model simulations under different chemotherapy scenarios.

DISCUSSION

This study systematically evaluated the chemoth-erapybased control effects on hookworm and ascariasis prevalence and intensity based on field observations and modeling. Our analyses help to optimize the chemotherapeutic scheme aiming at reducing ascariasis and hookworm infections in highly endemic areas, and direct the establishment of soil-transmitted helminthiasis control and elimination criteria.

The model parameter estimation was based on actual field data, including not only the "one stool three examinations" of 4833 persons in the two sites at baseline and after one year using the Kato-Katz method, but also worm extraction and differentiation after stool collection from each subject over three continuous days, which guaranteed a precise and robust estimation of model parameters. An indicator of the average number of parasites harbored in subjects (mean worm burden) was acquired in this study, which is seldom achieved in previous published studies[26]. Egg per gram (EPG) is no longer used for estimating the intensity of infection.

The density-dependent constraint on worm fecundity Z ($Z = e^{-\gamma}$) related to parasite burden is difficult to estimate[27-34]. The higher the parasite burden, the weaker the fecundity of adult worms, which means the higher the density-dependence effect. Equation (6) ($\lambda_{\bar{n}} = \lambda_0 e^{-\gamma\bar{n}}$) is based on a perfect situation of a field survey that acquires the number of all adult worms harbored in hosts and the average number of eggs laid by the adult worms. Because it is common that a stool examination shows positive while no female worms are extracted, or that EPG is high while few female worms are extracted, due to drug efficacy or some other reason, the density-dependent constraint on worm fecundity Z is likely to be more than 1, which is infeasible in actual model application. This paper proposes a method to modify the equation, which makes Z less than 1 and meet the relationship between it and other parameters like worm burden. Its rationality was validated by the accordance between model prediction and actual results.

The ascariasis infection rate in the survey participants after one year was higher than that at baseline in Cuiping of Sichuan, possibly due to a high proportion of participants who were lost to follow-up (because of non-compliance in negative infected subjects or migrant workers). Meanwhile, the basic reproductive rate (R_0) was near three in this site, which means that the reinfection rate would possibly be very high. Although the model predicted that the ascariasis infection rate after one year was lower than that at baseline, the predictions were consistent with the trends of ascariasis in Jinxian of Jiangxi and of hookworm in both sites.

The simulations indicated that it would take too long to reduce the prevalence to the criteria by taking annual chemotherapy in highly endemic areas. This suggests that (1) a combination of higher treatment coverage and frequency would have better effects, taking available resources and practical conditions into consideration; and (2) to control and eliminate soil-transmitted helminthiasis, chemotherapy control alone is not enough; a comprehensive control strategy is needed, including health education and environmental improvement.

The model prediction was based on the assumption that community environmental conditions would not change in the period of prediction. Once residents' hygienic behavior habits or environmental sanitation change, the model parameters will also change[35]. In this study no other measures were taken at the two sites during the one year follow-up period. Some provinces and areas in China are now dedicated to controlling soil-transmitted helminth infection through comprehensive control strategies like health education, chemotherapy, water and toilet renovation and environmental improvement[36]. What needs to be emphasized is that the effect of control measures besides chemotherapy should be taken into consideration (if they exist) in the model simulation for establishing control criteria. However, determining how to evaluate comprehensive effects requires further study.

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